In this reply I would like to answer those rejections as sited in the Office Action of April 11th 2003 as followed after an explanation of the background of the invention.

Background of the Invention: I would like to draw the kind attention of the Examiner to the fact that the invention is based on a known scientific fact that a compound with positron emitting molecule such as fluorine-18 will act as a "substrate" for metabolic uptake by cells in diseases such as cancer. The most common form is 18F-2-fluoro-2-deoxyglucose (FDG), which behaves like a common glucose molecule and be actively or passively transported into certain cells such as those in different types of cancer, heart, brain and kidney. The positron emitting compound is then trapped, producing radiation that is available for scanning and the detection of cancer (no prior art of such a concept in treatment before this invention). Such a fact is illustrated by the inclusion in line 19 of the original submission and in the two references (9) and (10).

"The substrate is taken up predominantly by malignant tumor tissues, infectious tissues, the myocardium, and the brain."

9. Phelps, M.E. et al., "Investigation of [18F] 2-fluoro-2-deoxyglucose for the measure of myocardial glucose metabolism," J. Nucl. Med. 19:1311-1319 (1978).

10. Gopal B. Saha et al., "Cyclotrons and Positron Emission Tomography Radiopharmaceuticals for Clinical Imaging," Seminars in Nuclear Medicine, Vol. XXII, No. 3 (July 1992), pp. 150-161.

The mechanism by which the positron emitting molecule and its associated compound is being captured by the target cell is by "substrate metabolism", which is a totally different concept from the "specialized monoclonal antibody and receptor or antigen" concept that has been implemented by all the papers from Mishani, Vessella and Lemelson. There are some differences in the Lemelson paper but it still involves an active monoclonal antibody element as a guide in addition to other nuclides interactions. To further illustrate this fact, the mechanism of metabolism of a substrate is like "consuming a special food when it is made available" while monoclonal antibody and antigen reaction is like a "lock and key" mechanism. I would like to amend claim 1 to reflect the specific action of this concept so that this invention is distinctly different from those prior art sited. In addition, some of the ways and the apparent ease of applying the

methodology sited from those articles could be used to overcome the 112 rejections in this invention.

Response to 103 Rejections:

A. claims 1, 14 and 19: Because of the change of claim 1, claim 1, 14 and 19 (under Lemelson) will specifically designate the invention to a delivery system by metabolism of a special substrate with the positron emitting compound. Since this field of science (the field of biochemistry and metabolism with simple compounds and small molecules) is totally, sufficiently and independently apart from the monoclonal antibody and antigen field (the field of immunology with complex and large molecules), this would form the basis that the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have NOT been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

The fact is also substantiated by a recently published article in Breast Cancer Research 2003, 5: R199-R205 (enclosed for your reference) by Moadel et al with essentially the same facts that I have presented in my invention 3 to 4 years ago. Since this article is published as a "Research Article" as recently as in 2003, the concept of using metabolism and substrate as a method of delivery of positron emitting compound is certainly NOT obvious to those studying the art of using monoclonal antibody and antigen published as old as 17 years ago (Lemelson in 1987).

B. claims 1,2, and 7-20: Please see the explanation above that the invention involves a totally different delivery system that would have eliminated the rejections under the prior art obviousness under Vesella, Lemelson and Mishani. For the prior art of Smith, the disclosure of radiopharmaceuticals labeled with these compounds are essentially for the purpose of diagnostics as "imaging" by scanners, and to predict the tumor response "after" chemotherapy treatment. Once again, there is no prior art disclosure of the use of positron emitting compounds working with "substrates" as treatment (except like above, with the monoclonal antibody antigen delivery system).

Response to 110 Rejections for Claims 1-20 :

As amended in the claim 1, the disease is restricted to cancer, and as such most cancer cells utilize the substrate described similarly as that described in the given case of renal cell carcinoma. The use of an imaging scanner that can detect these cancers before treatment was illustrated in the case of renal cell carcinoma. Such a scanner (positron emission tomography or PET) is now commonplace in any large size hospital anywhere in the United States for the diagnosis of "almost all" cancers. Once such an uptake of the substrate is demonstrated and by following the same principles described for renal cell carcinoma, it would be an easy enabling for any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As was also disclosed in Mishani et al and mentioned in the Examiner's Office Action, page 8 and 9 (4/11/2003), the treatment dosing is dependent on the severity and responsiveness of the condition to be treated and the optimum dosages, methodologies and repetition rates could be easily calculated by those persons skilled in the art. The delivery system is totally different between this invention and the one from Mishani, but once delivered, the treatment schedules, etc. would be similar since both involve more or less the same radioactive molecules.

Further demonstration was also illustrated by the obviousness of the treatment method proposed by Moadel et al in the article enclosed, which is essentially the same as described in this invention.

Details of the methodologies to use the invention in which most (except the delivery part from this invention by a substrate compound with positron emitting molecules) have been known by prior art:

The synthesis of ^{18}F-2-fluro-2-deoxyglucose (FDG) follows a familiar procedure reported in the literature (Hamacher et al., J. Nucl.Mec.27, 235-238 1986 and a copy of the paper is enclosed to you previously). The ^{15}O water target is bombarded with protons in the cyclotron. In the Applicant's case, it was done by a MiniTrace cyclotron manufactured by General Electrics. The resulting ^{18}F water is shunted, via a polyetheretheketone tubing to a FDG micro-laboratory module where the actual synthesis process occurs. The resulting FDG is collected in a sterile vial, checked for quality control, and then delivered in lead shielded syringes in unit dose format for

the use by physicians on their patients. A copy of the standard procedures and the various methods of quality control are enclosed previously for the examiner's review.

Typically FDG can be purchased nowadays easily in most western countries including the United States. With a half life of 110 minutes, cyclotron centers are now being established in most major metropolitan cities for the supply of FDG for diagnostic use of PET (Positron Emission Tomography) centers. FDG has been cleared by the FDA for human use and there has never been any serious reactions reported in its use for nearly twenty years. In essence, any person skilled in the art can order a specific dose of FDG with the local cyclotron center with a delivery service.

To carrying out the invention as stated in the treatment of cancer using positron emitting compounds such as FDG, ^{18}F-fluorocholine and methyl-^{11}C choline, a person or a physician licensed in the practice of oncology or radiotherapy in this case, has to calculate the effective dose required for these compounds to work. FDG is chosen in this respect to set as an example. The effective dose estimates for radiopharmaceuticals such as FDG per unit of mCi for different human organs have been calculated. A table composed by the Oak Ridge Institute For Science and Education has previously been enclosed for your information.

Initially the patient has to undergo a normal PET scan to determine the staging of the disease, the amount of cancer in approximate volume and the so-called Standard Uptake Value of FDG (SUV). SUV is defined as the uptake value of FDG in the tumor over the standard of the baseline tissues of the body per unit volume. From the Oak Ridge table one can see that the effective dose equivalent (EDE) of baseline general body tissue is about 1.5 rem/15m Ci, the 15mCi being the general high limit of a diagnostic dose of FDG. For cancerous tumors, the EDE is calculated conservatively by multiplying the SUV with the EDE of general tissue for the dose of mCi of FDG given. The reason why this is a conservative calculation is because if the SUV is high, for example, like those over 10, then there should be other local radiation effect from beta particles liberated from the positron carrying FDG. That means more EDE for the tumor. It has been estimated by a correspondence with V Gates of Ohio State University that a 1cm tumor with a 1% uptake of FDG can receive as much as 137.5 rems. But if one is to stay on the conservative side then the following formula will apply:

EDE of cancerous tumor = EDE of general body tissue x SUV in rems

If we estimate that general body tissue will receive 0.1 rem per mCi of FDG, the formula will be

EDE of cancerous tumor = Number of mCi given x 0.1x SUV in rems

In the case of FDG, the EDE in rems will be equal to the same in cGy, so the formula can simply be applied as

EDE of cancerous tumor = 0.1 Number of mCi x SUV in cGy

In the case that we have here with the renal cell carcinoma, a dose of 30mCi was given and the SUV is 10, then the

EDE of that renal cell carcinoma received was at least 0.1x30x10 = 30cGys

For those that want to use the invention to treat a case of cancer, the most common form of combination is with radiation therapy. So if for each fraction of radiation therapy of a standard 200cGy given and with the concurrent use of this invention for a renal cancer as illustrated, the actual delivered dose to the tumor is at least 200cGys + 30cGys (from the FDG given) = 230 Gys. The actual amount of increase which is 15% actual will have an effective radiation dose much higher than that. For the practicing radiotherapist, the actual effective dose, taken into effect of the shoulder effect of radiation and the accelerated effect of a higher dose fractionation, will be close to 20 to 30% higher for a similar course of 200cGys given for a total of 20 to 25 fractions, for example. Such an increase will be very significant and will enable an "actual curative dose" to only the cancerous part of the tumor but not to other vital organs such as the heart or major arteries surrounding the tumor. In practice, and because of the safety of FDG (which is essentially sugar solution with positron radiation), radiotherapists can, and should, easily adopt the combination of safe doses of FDG with their daily fractions of radiation for the treatment of cancers. If successful, any cancers that are not supposed to be cured easily by radiation alone can now have a second chance. Side effects will be spared to major organs. Radiation in high doses will be delivered only to cancerous tumors.

For the argument that only renal cell carcinoma can be treated by the suggestion in the invention, it should be kindly reminded the FDG is located to nearly 90% of the most common cancers with avidity and robust activity. As a matter of fact, most of the other cancers actually metabolize more FDG and therefore have a higher SUV than renal cell carcinoma. Medicare of the United States has now approved usage of FDG for PET scanning in tumors

like lung cancer, breast cancers, melanoma, lymphomas, colon cancers and head and neck cancers etc. Other common cancers are well under way to be included as standard care diagnosis eligible for Medicare reimbursements. As such, FDG is therefore proven to accumulate successfully in most common cancers. This invention will add the therapeutic approach of this molecule to all these cancers with very few, if any, experimentation necessary by those skilled in the art.

Amended Claims "Currently amended":

CLAIMS

What is claimed is:

1. A method of treating cancer ~~a disease~~ in a subject, comprising: administering a therapeutically effective amount of a positron-emitting compound which, specifically and only, acts as a substrate for metabolism as a method of delivery to the cancer cell of ~~to~~ the subject, wherein the positron emitting compound comprises one or more atoms of fluorine-18, carbon-11, nitrogen-13, or oxygen-15.

2. The method of claim 1, wherein the positron-emitting compound comprises one or more fluorine-18 atoms.

3. The method of claim 2, wherein the positron-emitting compound is ^{18}F-fluorodeoxyglucose.

4. The method of claim 3, wherein the ^{18}F-fluorodeoxyglucose is ^{18}F-2-fluoro-2-deoxyglucose.

5. The method of claim 2, wherein the positron-emitting compound is ^{18}F-fluorocholine.

6. The method of claim 1, wherein the positron-emitting compound is [methyl-^{11}C] choline.

7. The method of claim 1, wherein the positron-emitting compound is administered to the subject in a dosage at least about 1.5 times that used for diagnostic purposes.

8. The method of claim 7, wherein the positron-emitting compound is administered to the subject in a dosage at least about twice that used for diagnostic purposes.

9. The method of claim 1, wherein the positron-emitting compound is administered to the subject in a dosage of about 30 to 100 mCi per 50 kg of body weight.

10. The method of claim 1, wherein the positron-emitting compound is administered to the subject in a dosage of about 30 mCi per 50 kg of body weight.

11. The method of claim 1, wherein the positron-emitting compound is administered to the subject in a dosage of about 50 mCi per 50 kg of body weight.

12. The method of claim 1, wherein the positron-emitting compound is administered to the subject in a dosage of about 100 mCi per 50 kg of body weight.

13. The method of claim 1, further comprising administering any one of or any combination of immunotherapy, surgery, or other chemotherapy or radiation therapy to the subject at any stage in the treatment of the subject.

14. The method of claim 1, wherein the positron-emitting compound is administered intravenously.

15. The method of claim 1, wherein the positron-emitting compound is administered in one or two doses per day over five to ten days during a two-week to three-week period.

16. The method of claim 4, wherein the positron-emitting compound is administered in one or two doses per day over five to ten days during a two-week to three-week period.

17. The method of claim 15, wherein the doses are administered on five to ten consecutive days.

18. The method of claim 15, wherein the doses are administered on non-consecutive days.

19. The method of claim 1, wherein the disease is cancer.

20. The method of claim 19, wherein the cancer is bone cancer.

Conclusion:

I hope that the previous rejections under 103 and 112 for those specified claims from the Examiner have been addressed in this letter. I will try to contact the examiner in the coming week to clarify the issues raised and answers submitted. Should the Examiner have any questions, she is invited to contact the undersigned inventor at telephone number 852-9328-6768 (mobile in Hong Kong) or email alex.yeung@plasma-gene.com

Dated: March 23, 2004

Respectfully submitted

By:________________________

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